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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Lisa B. Arthur
Group	:	1655
Applicants	:	Bernard F. Mach et al.
Serial No.	:	08/484,786
Filed	:	June 7, 1995
For	:	DNA SEQUENCES CODING FOR THE DR B-CHAIN LOCUS OF THE HUMAN LYMPHOCYTE ANTIGEN COMPLEX AND POLYPEPTIDES, DIAGNOSTIC TYPING PROCESSES AND PRODUCTS RELATED THERETO

DECLARATION OF RICHARD LATHE, D.Sc.
UNDER 37 C.F.R. § 1.132

I, Richard Lathe, D.Sc., hereby declare and state as follows that:

1. I am a Research Professor at the Centre for Genome Research and Centre for Neurosciences, University of Edinburgh in Edinburgh, Scotland. During the period of 1989 to 1995, I served as Director of the Centre for Genome Research.

2. I hold the degrees of D.Sc. Molecular Biology, Hons. 1st Class, Department of Molecular Biology, University of Edinburgh, United Kingdom and Docteur es Sciences (Biologie Moleculaire), La Plus Grande Distinction, Laboratoire de Genetique, Universite Libre de Bruxelles, Belgium.

3. As detailed in my curriculum vitae, attached as Exhibit A, from September 1973 to date I have carried out extensive research in the field of molecular biology in the course of my scientific training, research and employment. As a result of that research, I have gained first-hand, practical experience in the use of synthetic oligonucleotides in the analysis of nucleic acids. I also have extensive practical experience in the preparation and screening of cDNA and genomic libraries of DNA sequences. More particularly, my practical experience includes performing hybridization assays wherein single-stranded DNA or RNA molecules associate to form double-stranded polynucleotide chains.

My work is exemplified by the bibliography included in Exhibit A. As indicated in that bibliography, during the period from 1976 to present, I authored numerous scientific publications relating to my work involving the application of recombinant DNA technology in the biomedical area. That work is detailed in the review article: R. Lathe, "Synthetic Oligonucleotide Probes Deduced From Amino Acid Sequence Data - Theoretical and Practice Considerations", J. Mol. Biol., 183, pp. 1-12 (1985), Exhibit B hereto. Further details of my educational and research career are set forth in Exhibit A.

4. I am given to understand that United States patent application 08/484/786 ("the '786 application") and United States patent application 08/486,804 ("the '804 application") share the same invention disclosure. Specifically, the '786 application

and the '804 application are both divisional applications of United States patent application Serial No. 07/902,999 (filed June 23, 1992, now United States patent 5,503,976), which is a divisional of United States patent application Serial No. 06/518,393 (filed July 23, 1983, now United States patent 5,169,941). I am also given to understand that the both the '786 application and the '804 application claim an earliest priority date of July 30, 1982.

5. I have read and considered the '804 application, which I understand shares the identical disclosure of the '786 application, that was filed in the United States Patent and Trademark Office on June 7, 1995. A copy of the '804 application is attached as Exhibit C. I have read and considered the July 21, 2000 Office Action in the '786 application ("the Office Action"), attached hereto as Exhibit D. I have also read and considered claims 51 to 75 of the '786 application ("the claims of the '786 application"), which I am informed and believe to have been pending as of the date of the Office Action. A copy of those claims is attached as Exhibit E.

6. In the present declaration, I address the following issue raised in the Office Action -- Whether, given the specification of the '786 application (which is identical to '804 application, which I have reviewed) and the state of the art as of its July 30, 1982 priority date, a person of skill in the art would recognize and be able to obtain nucleic acid molecules

useful in the HLA-DR typing process and kits encompassed by the invention of the claims of the '786 application.

7. I consider a person of skill in the art to be one skilled in the art of hybridization-based molecular biology, including DNA hybridization, as of July 30, 1982 (hereinafter "a person of skill in the art"). Such a person would have had a Ph.D. degree at that time and several years of relevant laboratory experience.

In my opinion, given the specification of the '786 application and the state of the art as of its July 30, 1982 priority date, a person of skill in the art would be able to select the conditions of hybridization required to determine DNA sequences capable of hybridizing to a polymorphic region of the HLA-DR-ß chain locus of the human lymphocyte antigen complex for use in the HLA-DR typing process and kits according to the claims of the '786 application, without undue experimentation. As such, a person of skill in the art would be able to select a class of DNA sequences capable of hybridizing to the DNA sequences recited in the claims of the '786 application for use in such processes and kits.

8. Based on my reading of the disclosure of the '786 application and my knowledge of hybridization-based molecular biology, I do not believe that a person of skill in the art would have to carry out undue experimentation to determine the conditions of hybridization (i.e. salt and buffer concentration, pH and temperature) or lengths of nucleic acids that would

hybridize to the particular sequences recited in the claims of the '786 application. As a result, I believe that a person of skill in the art would be able to determine which nucleic acid molecules would or would not hybridize to those sequences and, therefore, what nucleic acid molecules are useful in the HLA-DR typing process and kits encompassed by the invention of the claims of the '786 application.

9. A person of skill in the art would understand the term "hybridizing" as used in the claims of the '786 application to refer to the association of two single-stranded nucleic acids to form a paired duplex hybrid. More specifically, a person of skill in the art would understand that term to denote the use of hybridization assays to detect or select DNA sequences capable of binding to or pairing with one of the specific DNA sequences recited in those claims. Thus, a person of skill in the art would understand the phrase "DNA sequences being capable of hybridizing" as used in the claims of the '786 application to refer to DNA sequences that would be detected or selected in a conventional hybridization assay as a result of their binding to or pairing with one of the specific DNA sequences recited in those claims.

10. On July 30, 1982, such hybridization assays were of such routine nature in molecular biology laboratories that they were normally carried out by a technician. In my opinion, such assays would not involve undue experimentation. See, for example, Astell et al., Biochemistry 12, 5068-5074 (1972)

[Exhibit F] and Szostak et al., Methods Enzymol. 68, 419-428 (1979) [Exhibit G]. Thus, the selection of conditions of hybridization required to carry out the invention of the claims of the '786 application would not require undue experimentation.

11. In my opinion, as of July 30, 1982, the concept of hybridization was well defined in the art, as "the pairing of two complementary or nearly complementary DNA strands to form a stable duplex". See, for example, Astell [Exhibit F] and Szostak [Exhibit G]. It was also known that the efficiency of such pairing is a function of both the temperature of the hybridization medium (which tends to dissociate the duplex) and the salt concentration of the medium (which tends to associate the duplex). Thus, at any given salt concentration, there is a particular temperature at which the two DNA strands of the hybrid duplex will dissociate from one another. This dissociation was referred to as "melting" and the temperature of melting was designated the "Tm" of the hybrid under the given salt conditions (see Bonner et al., J. Mol. Biol. 81, 123-135 (1973) [Exhibit H]).

12. As of July 30, 1982, for a particular salt concentration, it was possible to calculate the Tm of a hybrid duplex. As set forth in Bonner, as a result of a large number of empirical observations, an equation, known as the Schildkraut and Lifson reaction, was developed that permitted estimation of Tm at any given salt concentration:

$$Tm = 81.5 + 0.41(\%G+C) + 16.6(\log M) - 0.72(F\%)$$

wherein:

Tm = temperature of melting in Celsius degrees

(%G+C) = G/C content of DNA

M = salt (monovalent cation) concentration in moles/liter

F = formamide concentration (volume/volume).

Theoretically, for effective hybridization, one could use any temperature below the Tm estimated by the Schildkraut and Lifson reaction, to obtain a stable hybrid. However, in practice, the rate of hybridization is strongly dependent upon the particular temperature below Tm employed. In the definitive experiments of Bonner, the rate of hybridization was measured at various temperatures ranging from Tm-7 to Tm-50. These data are depicted in Figure 8 of the article. They show that the rate of hybridization reaches a peak between Tm-20 and Tm-27. From the breadth of the peak, it can be seen that hybridization temperatures of Tm-15 and Tm-30 give hybridization rates of over 90% of the maximum rate. Other experiments described in Bonner demonstrated that as the hybridization temperature decreases below Tm-27, the specificity of the hybridization progressively worsens. Thus, as a result of Bonner's experiments, an optimal range of hybridization conditions was defined to be from about Tm-20 to Tm-27.

13. As of July 30, 1982, a person of skill in the art would appreciate that salt and temperature conditions that result in the range of Tm-20 to Tm-27 would be one example of

conventional hybridization conditions capable of effecting correct base pairing between nucleotide strands. That person would be able to employ the teachings of Bonner in order to determine the temperature, salt, pH, and buffer regimen to carry out hybridization to obtain DNA sequences useful in the HLA-DR typing process and kits of the claims of the '786 application. For example, as exemplified at page 31, lines 23-30 of that application, hybridization of short (19 nucleotides) oligonucleotide DNA fragments was achieved under conditions illustrated in Conner et al., Proc. Natl. Acad. Sci. USA 80, 278-282 (1983) [Exhibit I].

14. A person of skill in the art would recognize that Bonner describes the classic formula by which to calculate the effect of mismatches on the stability of long DNA hybrids. That person would have appreciated that this same formula could be applied to the formation of DNA hybrids involving short nucleotide sequences. Accordingly, with the '786 disclosure in hand, and in view of knowledge in the art as of the priority date of the '786 application, it is clear that a person of skill in the art could readily select the appropriate conditions for hybridization to carry out the invention of the claims of the '786 application.

15. Hybridization assays, as developed through the 1970's, often consisted of dissociating two double-stranded nucleic acids, commonly DNA, at high temperature. The two samples were then cooled to a temperature allowing reassociation,

mixed, and allowed to form hybrids ("hybridization"). The degree of hybridization informs the researcher as to the extent of similarity or "homology" between the two nucleic acid samples. More commonly, and by July 30, 1982, hybridization protocols typically employed an unknown "target" polynucleotide and a known "probe" polynucleotide. For the purposes of the present declaration, the term "homology" or "homologous" is used interchangeably with "complementarity" or "complementary" to denote the capacity of a nucleic acid to form a hybrid duplex with another nucleic acid <u>or its complementary strand.</u> In other words, when probe and target are homologous, a hybrid duplex may be formed.

16. The end-point of a hybridization assay is to determine the degree of homology between probe and target. A critical feature of hybridization assays is thus <u>discrimination</u>. In other words, the experimental conditions are set (1) to allow the probe to hybridize with a small number of pre-defined target sequences; and at the same time (2) to ensure that the probe fails to hybridize with the numerically superior class of sequences that occur by chance in a nucleic acid sample but which are unrelated to the probe.

17. As described below, the hybridization conditions employed with this aim in mind differ as a function of the probe. On July 30, 1982, it was generally recognized, as it is today, that there are two types of hybridization protocols. The first comprises the hybridization of long (e.g. >50 nucleotides in

length) homologous sequences. I refer to this protocol as the "long" protocol. The second comprises the hybridization of short (e.g. 10-25 nucleotides) matching sequences. I refer to this protocol as the "short" or "oligonucleotide" protocol, because short, often synthetic, DNA (or RNA) molecules are commonly referred to as "oligonucleotides" or sometimes "primers". See, for example, Smith, Nucleic Acids Symp. Ser. 387-395 (1980) [Exhibit J].

18. The thermal stability of a duplex nucleic acid is dependent on a number of parameters, all of which were well known to a person of skill in the art as of July 30, 1982. These include, in addition to the salt and buffer concentration, pH, temperature, the degree of base-pairing between probe and target nucleotides and the length of the duplex that can be generated. A long probe molecule generates a long hybrid molecule that is stable if a small number of incorrect base-pairs ("mismatches") are included in the duplex. By contrast, a short probe generates a short hybrid that can be critically destabilized by even one or two mismatches. See for example, Zoller & Smith, Nucleic Acid Res. 10, 6487-6500 [Exhibit K] and Gillam & Smith, Gene 8, 99-106 [Exhibit L].

19. In my opinion, a person of skill in the art as of July 30, 1982 would appreciate that conditions of hybridization for DNA sequences useful in the HLA-DR typing processes and kits according to the claims of the '786 application pertain to the

"short" hybridization protocol. Such is the case because the nucleic acid sequences recited in those claims, and the amino acid sequences to which they correspond, both fall within the class of short or oligonucleotide hybridizations.

20. To carry out a hybridization assay as described in the '786 application, it is my belief that a person of skill in the art, being aware of the length of the probes, would inevitably select the short protocol to determine whether a sample of nucleic acid contained "DNA sequences being capable of hybridizing" to the DNA sequences recited in the claims of the '786 application. The conditions for such oligonucleotide hybridization were well established in the prior art as of July 30, 1982. See Astell [Exhibit F]; Szostak [Exhibit G]; Smith [Exhibit J]; Zoller & Smith [Exhibit K] and Gillam & Smith [Exhibit L].

21. More particularly, the prior art had reported conditions under which short oligonucleotide probes would hybridize with perfectly matched sequences (i.e., 100% homology) but not with DNA sequences containing one or more mismatches (i.e., less than 100% homology). For example, Szostak [Exhibit G] had described the hybridization of 12-mer oligonucleotides corresponding to bacteriophage lambda DNA that either matched the probe completely (wild-type) or contained single mismatches (mutant). Szostak [Exhibit G] also described hybridization conditions under which only the wild-type probe hybridized. In

addition, Wallace et al., <u>Nucleic Acid Res.</u> 9, 3647-3656 (1981). [Exhibit M] reported hybridization conditions under which a 19-mer oligonucleotide probe containing a single base substitution corresponding to the human beta-globin gene (HβS-sickle cell anemia) hybridized to only HβS DNA and not to DNA of the normal HβA allele. And <u>Conner</u> [Exhibit I] reported specific detection of sickle cell β-globin DNA using a 19-mer oligonucelotide probe; describing in detail the conditions that permit detection of single or multiple mismatches.

22. In view of such understanding in the art as of July 30, 1982, it is my belief that a person of skill in the art could carry out a hybridization assay according to the '786 application by preparing a filter carrying DNA sequences of the target sample together with controls. Some would be negative controls: consisting of an assortment of DNA sequences other than HLA-DR-ß DNA sequences, for instance DNA sequences coding for HLA-ß or any other unrelated DNA sequences. Some would be positive controls: consisting of known HLA-DR-ß DNA sequences, such as those described in the '786 application and deposited in connection therewith. That person of skill in the art would then prepare a hybridization probe from the DNA sequences of the claims of the '786 application using conventional techniques. And that person would expose the DNA sequences on the filter to that probe under a series of experimental hybridization conditions. The conditions chosen for the assay would be estimated from the prior art, but adapted to local laboratory

conditions, so that hybridization would occur with the positive controls, but not with negative or background controls, so as to address the identity of the target DNA sample with respect to the chosen probe.

23. I am of the opinion that a person of skill in the art, as of July 30, 1982, taking into account the disclosure of the '786 application, the literature cited therein (Conner [Exhibit I]), as well as additional prior art (see, for example, Astell [Exhibit F]; Szostak [Exhibit G]; Smith [Exhibit J]; Zoller & Smith [Exhibit K] and Gillam & Smith [Exhibit L]), would be able to select the appropriate conditions for hybridization to carry out the invention recited in the claims of the '786 application without undue experimentation, using conventional hybridization techniques. As a result, a person of skill in the art would be able to select a class of DNA sequences capable of hybridizing to the DNA sequences recited in the claims of the '786 application to carry out HLA-DR typing and to use HLA-DR typing kits according to the '786 application.

24. I hereby further declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18, United States Code, and that such willful false statements may

jeopardize the validity of this application and any patent issuing thereon.

RICHARD LATHE, D.Sc.

Signed this ___ day

of _________, 2001

at Edinburgh, Scotland, United Kingdom

CURRICULUM VITAE

Jack L. Strominger

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Date of Birth: New York City, August 7, 1925

Marital Status: Married, four children

Education: Harvard, 1942-1944, A.B., 1947
Yale, 1944-1948, M.D., 1948

Positions:

1948-1949	Intern (Medicine) at Barnes Hospital, St. Louis.
1949-1950	Research Fellow of the American College of Physicians, Department of Pharmacology, Washington University School of Medicine, St. Louis.
1950-1951	Research Assistant, Department of Pharmacology, Washington University School of Medicine, St. Louis.
1951-1954	Senior Assistant Surgeon, U.S. Public Health Service at National Institute of Arthritis & Metabolic Diseases, Bethesda.
1955	On leave of absence at Carlsberg Laboratory, Copenhagen, Denmark & Molteno Institute, Cambridge University, England. Fellow of the Commonwealth Fund.
1955-1958	Assistant Professor of Pharmacology, Department of Pharmacology, Washington University School of Medicine, St. Louis, Markle Scholar in Medical Science.
1958-1960	Associate Professor of Pharmacology, Department of Pharmacology, Washington University School of Medicine, St. Louis, Markle Scholar in Medical Science.
1960-1961	Professor of Pharmacology, Department of Pharmacology, Washington University School of Medicine, St. Louis. Forsyth Faculty Fellow, 1960.
1961-1964	Professor of Pharmacology & Microbiology, Departments of Pharmacology & Microbiology, Washington University School of Medicine, St. Louis.
1964-1968	Professor of Pharmacology & Chemical Microbiology, University of Wisconsin Medical School, Madison. Chairman of the Department of Pharmacology. Member of the University Committee on Molecular Biology.

1968-Present Professor of Biochemistry, Department of Biochemistry & Molecular Biology (now called Department of Molecular and Cellular Biology), Harvard University, Cambridge, Mass.

Chairman, Department of Biochemistry & Molecular Biology, 1970-1973.

Director of Basic Sciences, Sidney Farber Cancer Center, 1974-1977 (now called Dana-Farber Cancer Institute) & member of the Department of Cancer Immunology and AIDS, 1977 - present.

Higgins Professor of Biochemistry, 1983-present .

Advisory Committees:

Board of Scientific Counselors, NIAMDD, NIH
Scientific Advisory Committee of the Ludwig Cancer Research Institute,
Lausanne Scientific Advisory Committee of the Max-Planck Society
Steering Committee of the Biomedical Sciences Scientific Working Group, World Health Organization
Scientific Advisory Committee of the Humboldt Foundation

Awards and Honors:

Borden Undergraduate Research Award in Medicine, Yale University, 1948
John J. Abel Award in Pharmacology, 1960
Paul-Lewis Laboratories Award in Enzyme Chemistry, 1962
American Academy of Arts & Sciences (elected 1968)
National Academy of Sciences Award in Microbiology in honor of Selman Waxman, 1968
National Academy of Sciences (elected 1970)
Guggenheim Fellowship, 1974-1975
D.Sc. (hon.) Trinity College, Dublin, 1975
National Institute of Medicine (elected 1975)
Rose Payne Award, Amer. Soc. for Histocompatibility & Immunogenetics, 1986
D.Sc. (hon.) Washington University, St. Louis, 1988
Assoc. European Molecular Biology Organization (Foreign Member) 1990
Hoescht-Roussel Award, American Soc. for Microbiology 1990
Pasteur Medal in Gold 1990
Newton-Abraham Research Professor, University of Oxford 1991
M.A. Univ. of Oxford 1991
D.Sc. (hon.) Albany Medical College 1991
Cancer Research Institute Award in Fundamental Immunology 1992
Sandoz Prize in Immunology, 1992
Roche Institute of Molecular Biology V.D. Mattia Award, 1992

Claire W. & Richard P. Morse Award, Dana Farber Cancer Institute, 1992
Passano Foundation Award, 1993
American Philosophical Association (elected 1994)
Albert Lasker Basic Medical Research Award, 1995
Paul Ehrlich Prize,1996
Novartis-Drew Award, 1997
Japan Prize, 1999
Klemperer Award, 1999
Kaj Linderstrom-Lang Prize, 1999

Society Memberships:

American Society of Biochemistry and Molecular Biology
American Association for Advancement of Sciences
American Association of Immunologists
American Society of Microbiologists
American Society of Pharmacology & Experimental Therapeutics
American Chemical Society
Sigma Xi
Alpha Omega Alpha

United States Patents:

US 6,322,979	Molecular recognition at surfaces derivatized with self-assembled monolayers.
US 6,313,263	γ/δ T cell receptor and methods for detection.
US 6,291,645	p62 polypeptides, related polypeptides, and uses therefor.
US 6,197,515	Molecular recognition at surfaces derivatized with self-assembled monolayers.
US 6,162,609	Diagnostic and therapeutic methods based upon V α 24J α Q T cells.
US 5,962,224	Isolated DNA encoding p62 polypeptide and uses therefor.
US 5,908,762	Transcription factor regulating MHC expression CDNA and genomic clones encoding same and retroviral expression constructs thereof.
US 5,880,103	Immunomodulatory peptides.
US 5,874,531	Identification of self and non-self antigens implicated autoimmune disease.
US 5,840,832	Transcription factor regulating MHC expression CDNA and genomic clones encoding same and retroviral expression constructs thereof.
US 5,827,516	Immunomodulatory peptides.
US 5,620,850	Molecular recognition at surfaces derivatized with self-assembled monolayers.
US 5,601,822	γ/δ T cell receptor and methods for detection.

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Education and Employment

1969-73:	B.Sc. Molecular Biology, (Hons. class 1). University of Edinburgh
1973:	Technical Officer, MRC Molecular Genetics Unit, Edinburgh
1973-6:	Docteur ès Sciences (class 1). Laboratory of Genetics, Free University of Brussels [Ciba-Geigy Fellowship]
1977-9:	EMBO Fellow, Institute of Molecular Genetics, University of Heidelberg, Germany
1979-81:	Senior SRC Fellow, Department of Genetics, University of Cambridge
1981-4:	Assistant Scientific Director, Transgène S.A., Strasbourg, France
1984-5:	Principal Scientific Officer and Head, Molecular Biology Department, ARC Animal Breeding Research Organisation, Edinburgh
1985-6:	Group Leader, Laboratory of Eukaryotic Molecular Genetics (LGME), University of Strasbourg, France
1986-89:	Professor of Genetics/Genetic Engineering, University of Strasbourg (tenured); Group Leader, LGME; Director/Scientific Director, Ecole Supérieure de Biotechnologie de Strasbourg (ESBS), France
1989-	Research Professor, Centre for Genome Research and Centre for Neuroscience, University of Edinburgh (Director, Centre for Genome Research, 1989-95)

Publications. R. Lathe

Published papers

Lecocq, J.P., Dambly, C., Lathe, R., Babinet, C., Bailone, A., Devoret, R., Gathoye, A.M., Garcia, H., Dewilde, M and Cabezon, T. (1976). Nomenclature and location of bacterial mutations modifying the frequency of lysogenisation of *E. coli*. Molec. Gen. Genet. **145**, 62-63.

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